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March 1, 2002

**VIA OVERNIGHT MAIL**

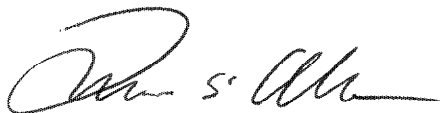
Dockets Management Branch  
Food and Drug Administration  
Department of Health and Human Services  
Room 1061, HFA-305  
5630 Fishers Lane  
Rockville, MD 20857

**Re:   Docket No. 01P-0546/PSA 1**  
**Amendment to Petition for Stay of Agency Action**

Dear Madam or Sir:

On behalf of our client, Pharmacia Corporation and its affiliate G.D. Searle ("Pharmacia"), and pursuant to 21 C.F.R. § 10.35, we request that the Commissioner of the Food and Drug Administration consider the attached amendment to Pharmacia's petition for stay of agency action filed on December 7, 2001 and docketed by the Food and Drug Administration on December 10, 2001 (01P-0546/PSA 1). The attached amendment consists of the declaration of Edward D. Frohlich, M.D., M.A.C.P., F.A.C.C., signed and dated February 26, 2002.

Respectfully Submitted,



Kathleen M. Sanzo, Esq.  
Lawrence S. Ganslaw, Esq.  
Counsel for Pharmacia Corporation

cc:   Gary J. Buehler  
      Douglas Throckmorton  
      Janet M. Burroughs  
      William C. Lucas, Esq.  
      Richard S. Lev, Esq.  
      Stephen Paul Mahinka, Esq.

Attachment

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01P-0546

SUP 1

**DECLARATION OF EDWARD D. FROHLICH, M.D., M.A.C.P., F.A.C.C.**

Edward D. Frohlich, M.D., M.A.C.P., F.A.C.C., makes the following declaration:

1. I am the Alton Ochsner Distinguished Scientist at the Ochsner Clinic Foundation, New Orleans, Louisiana 70121. I also hold faculty appointments as Professor of Medicine and of Physiology at the Louisiana State University School of Medicine – New Orleans, and Clinic Professor of Medicine and Adjunct Professor of Pharmacology at Tulane University School of Medicine, New Orleans. I have recently completed an eight year extended tenure as Editor-in-Chief for the journal *Hypertension* from January 1995 through December 2001. A copy of my *curriculum vitae* and bibliography are attached. In brief, I have elected memberships in the American Physiological Society, American Society for Pharmacology and Experimental Therapeutics, American Society for Clinical Investigation, Association of American Physicians among others. I have also served as the Chairman of the Council for High Blood Pressure Research (of the American Heart Association), President of the American Society of Clinical Pharmacology, and Therapeutics, and President of the Society for Geriatric Cardiology. I have served as: a member of the Advisory Panel on Cardiovascular and Renal Drugs of the Food and Drug Administration; the Joint Coordinating Committee of the National High Blood Pressure Education Program (National, Heart, Lung and Blood Institute); Chairman of the Cardiovascular Sciences Study Section (National Institutes of Health); member of Veterans Administration and American Heart Association research grant-in-

aid study sections; and on the Advisory Committee for Cardiovascular Hypertensive Diseases of the World Health Organizations.

2. In my position with the Ochsner Clinic Foundation, I spend approximately 20-25 percent of my time in patient care, and approximately 75-80 percent of my time teaching, supervising and conducting research, primarily on hypertension and cardiovascular diseases. I am widely published in the area of hypertension and lecture often and widely on this topic. I am the author of over 900 peer-reviewed scientific papers and editor of several textbooks. As Editor-in-Chief of Rypins' Basic and Clinical Sciences Review (presently in its 18th Edition), I author the chapter of Internal Medicine, and I am sole author of the textbook Hypertension: Evaluation and Treatment. I have been an active co-participant of every Joint National Committee Report on the Detection, Evaluation and Treatment of Hypertension since 1972 and was a co-author of its preceding report in 1970-71. Finally, I have had extensive experience in counseling and treating patients for management of high blood pressure and angina pectoris and perform and continue to supervise and have a substantial clinical and preclinical research experience in hypertension and with antihypertensive therapeutic entities. I have published widely on preclinical and clinical studies involving each class of antihypertensive drugs since the introduction of the thiazide diuretics in the 1950s. My studies have dealt with the hemodynamic and other physiological actions of these drug classes and on the pathophysiology of the various hypertensive diseases.

3. In my personal experience and analysis of the literature dealing with Covera HS®, I believe the compound to be a reliable, safe, and effective agent for the treatment of hypertension and angina pectoris, and it has maintained a strong position clinically due to widespread physician and patient acceptance. I have had considerable experience using Covera-HS® (verapamil hydrochloride) and other verapamil formulations in my clinical practice and have prescribed this compound for a wide range of patients in order to obtain adequate control of their blood pressure and chest discomfort. In particular, I have used this agent with efficacy in those patients: with uncontrolled hypertension together with agents that suppress the renin-angiotensin system; taking diuretics or beta-adrenergic receptor blocking compounds; with high blood pressure and an unusual rapid heart rate; with bilaterally occlusive renal arterial disease (or occlusive renal arterial disease in a single kidney) in whom angiotensin converting enzyme inhibitors and angiotensin (type 1) receptor antagonists are contraindicated; and who have had side effects (physiological or metabolic) with other classes of antihypertensive drugs. I have also found it to be particularly effective in patients of the following demographic groups because of the demonstrated efficacy therein: the elderly, black patients, and those patients with certain gastrointestinal complaints (e.g., chronic frequent bowel movements).
4. Calcium antagonists, although sharing the common ability to inhibit the action of the calcium ion within myocytes of the cardiovascular system, possess vastly heterogeneous mechanisms of action ranging from the differential blockade of

one or more of the several calcium channel receptors of the differential blockade of intracellular targets as diverse as calcium-binding proteins, sarcoplasmic reticulum, and mitochondria. Therefore, this class of drugs exhibits vastly different clinical effects (e.g., nimodipine is beneficial in the treatment of cerebral bleeding, but it has little effect on blood pressure). Verapamil, the first calcium antagonist synthesized, has long been approved by FDA for the safe and effective treatment of hypertension and for angina pectoris because it reduces arterial pressure and also slows heart rate. These actions permit reduction in the “double product” (systolic pressure multiplied by heart rate), ventricular wall tension, and myocardial oxygen demand.

5. The clinical safety and efficacy of verapamil in the treatment of hypertension and angina pectoris is dependent on its relative affinities for the vast number of its potential extracellular and intracellular targets (vide supra see above). Alterations in the route and rate of administration of verapamil may also affect its bioavailability and, consequently, its desired clinical actions. For example, following its intravenous administration, it will rapidly slow heart rate in patients with supraventricular tachycardia. It is highly safe and effective in controlling heart rate, arterial pressure and clinical symptoms.
6. Covera-HS® has been shown to be unique among the verapamil products currently available in the United States because of its controlled-onset, extended-release (“COER”) delivery system. When it is taken at bedtime as labeled, the

COER system involves a 4-to-5 hour lag time in the release of verapamil so that its plasma level attains its maximum in the early morning hours – when blood pressure rapidly increases – and its minimum during the night – when blood pressure frequently falls to its lowest level of the normal circadian rhythm of arterial pressure.

7. Risk of myocardial infarction, sudden cardiac death, thrombotic stroke, and myocardial ischemia may be increased in the early morning due to the forestated natural circadian variation in hemodynamics and sympathetic tone. Upon awakening, a surge of adrenergic (or sympathetic) activity can increase heart rate and arterial pressure and may even promote hypercoagulability of circulating blood, thereby predisposing the patient to an increased likelihood of morbid and mortal cardiovascular events. Verapamil (i.e., the active compound released from Covera-HS®) reaches maximum plasma levels during early morning thereby addressing the rising arterial pressure in a manner which has been deemed safe and effective by FDA.
8. Furthermore, verapamil released from Covera-HS® reaches its lowest level during sleep, when blood pressure is usually at its lowest levels. This protects the patient from hypotensive events that may occur from high concentrations of verapamil. Thus, Covera-HS® has been demonstrated to remain safe and effective throughout the night by decreasing blood pressure and lowering heart rate. It has also been reported to restore the nighttime dip in blood pressure in

“non-dipper” essential hypertensive patients. Thus, the Covera-HS® delivery system has been shown to be timed to provide adequate control of arterial pressure over the entire 24 hour dosing period.

9. It therefore follows that multisource versions of Covera-HS® must mimic the COER delivery system’s ability to: (1) incorporate a 4 to 5-hour lag time of release; (2) establish, to a comparable rate and extent of release, maximal verapamil plasma levels during the early morning hours; and (3) establish, to a comparable rate and extent of release of verapamil plasma levels over the 24-hour period, a course of action that insures that the product is bioequivalent both pharmacologically and clinically.
10. Given the significant patient reliance on Covera-HS®, it is imperative that multisource versions accurately and precisely duplicate the innovator delivery system. The controlled- and timed-release of verapamil distinguishes Covera-HS® from other verapamil products. Accordingly, these unique release characteristics establish the need for generic formulations of Covera-HS® to be proven at least as safe and effective as the existing verapamil products, which have served as the basis for FDA’s approval of Covera-HS® as a new drug. The FDA cannot and must not assume that a multisource version of Covera-HS® that does match-up identically to the foregoing characteristics of the COER delivery profile will be as safe and effective as Covera-HS®. Consequently, the FDA properly should mandate bioequivalence requirements for these products that will

assure a precise comparison of verapamil release profiles and resulting clinical effects. These points are of particular clinical necessity at this time when physicians, third party reimbursers, and the pharmacy dispensers consider the formulations interchangeable.

11. The FDA must assure the safety of all drugs, whether pioneer or multisource. Patients taking Covera-HS® do so for important reasons – to avoid elevations of arterial pressure and development of angina pectoris during the early morning hours and throughout the day, thereby decreasing, in particular, the risk of early morning cardiovascular events. To ensure the public health and safety, any multisource version of Covera-HS® must be equivalent in terms of its safety, efficacy, and bioavailability for these same precise indications. The FDA should, therefore, mandate bioequivalence requirements that will prevent safety and efficacy failures of multisource formulations that could lead to an increased risk of early morning or other cardiovascular events. As the Agency is all too aware, these events may have life or death consequences.
12. Therefore, I strongly believe that the FDA properly should mandate pharmacodynamic and pharmacokinetic bioequivalence requirements to assure that all multisource products are clinically equivalent. In the case of Covera-HS®, bioequivalence requirements must assure that multisource products are equivalent with respect to their ability to control elevated arterial pressure and

chest pain, the two major indications for these life-threatening diseases for which this agent is prescribed.

13. Based on the foregoing statement, it is my opinion that the FDA should restrict approval of any application for multisource formulations of Covera-HS® only to those agents with strong and compelling evidence that establishes the bioequivalence of their formulations. Specifically, FDA should require that multisource formulations be equivalent to Covera-HS® on the basis of appropriate bioequivalence indices, including: (1) maximum serum drug (verapamil) concentration (" $C_{max}$ "); (2) area-under-the-concentration-time-curve from time zero to infinity (" $AUC_{0-\infty}$ "); and (3) partial AUC (from dosing to the time of maximum serum drug (verapamil) concentration) ( $T_{max}$ ). FDA traditionally requires generic products to be bioequivalent to pioneer versions on the basis of  $C_{max}$  and  $AUC_{0-\infty}$ . With respect to partial  $AUC_{0-T_{max}}$ , requiring multisource formulations of Covera-HS® to demonstrate equivalence for this parameter will assure that they have the same initial exposure and delayed delivery as Covera-HS®. That is, mandating bioequivalence in terms of partial  $AUC_{0-T_{max}}$  will insure that all multisource products duplicate Covera-HS®'s reduction of the morning rise in blood and heart rate. As discussed, the initial exposure and delayed delivery of Covera-HS® are crucial to the safety and efficacy of this formulation of verapamil. Moreover, the foregoing testing requirements will assure that all multisource products will have an equivalent extent and rate of release of verapamil during an entire twenty-four hours,


especially during the critical early morning hours. In the absence of these testing requirements and clinical necessities, and in particular a precise assessment of initial exposure/delayed delivery (addressed through an assessment of partial  $AUC_{0-T_{max}}$ ), there can be no assurance that this will be the case.

14. Consistent with the foregoing, I also support the bioequivalence standards requested in Pharmacia's Stay Petition to appropriately assess the equivalence of multisource versions of Covera-HS®, including:
  - Single-dose, duplicate design, fasting study of the highest strength product;
  - Food-effects and non-replicate design study of the highest strength product;
  - and
  - Nighttime dosing.
15. Patients in the U.S. must be able to rely, without question, upon their chosen method of blood pressure control. As a physician who has dedicated his professional career in the area of hypertension (which has spanned over 40 years) to addressing hypertension and other cardiovascular diseases, I appreciate the issue that cost savings which generic preparations might offer, but until their rate and extent of action and effectiveness have been demonstrated adequately, the initial cost savings may be negated by the ultimate costs of inadequately controlled blood pressure and other disastrous consequences of hypertensive disease. I am troubled at the prospect of patients and physicians being provided with less effective multisource formulations of Covera-HS® (or any other

therapeutic agent). In light of the significant public health ramifications, the testing requirements discussed herein are essential to assure that less effective formulations do not become available for patients in the United States, and the patient health is not compromised by the risk of inadequately controlled blood pressure.

I declare under the penalty of perjury that the foregoing is true and correct:

Executed on February 26, 2002

  
Edward D. Frohlich, M.D., M.A.C.P., F.A.C.C.

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